INHERITANCE OF CONGENITAL PALSY IN GUINEA-PIGS[1]

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INTRODUCTORY

IN 1914 a litter of two guinea-pigs was born in our laboratory, one of which differed from the other in that it appeared to lack nervous control. When this individual was placed on its feet, attempts on its part to walk resulted in spasmodic stiffening of the legs, causing it to fall over on its side, where it lay helpless and unable to get up. Although the animal appeared otherwise in good physical condition, it was thought at the time that the trouble might be due to temporary nutritional disurbance, and attempts were accordingly made to feed it by hand,

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until it should be able to nurse. The effort was, however, unavailing, the subject gradually becoming weaker and the symptoms more pronounced, until death ensued in a few days. A second litter was produced by this pair on May 19, 1914. This consisted of three young, which appeared in all respects normal. On August 27, however, another litter of two was produced and one of these was like the abnormal individual described above. This gave rise to the suspicion that the defect might be due to some hereditary cause and consequently the mating of the same parents was continued, with the following results: November 6, 1914, one defective offspring; March 24, 1915, three offspring, 2 being normal and one born dead; and June 20, 1915, 2 normal, 1 defective and 1 born dead. Not counting the two born dead, since their condition with respect to normal reactions could not be determined, this pair then produced a total of 13 young, of which 9 were normal and 4 defective. These results not only strengthened the presumption that we had to deal with a heritable condition, but were so close to a three-to-one ratio as to suggest that it might be a simple Mendelian recessive. It may be stated at this point that further extensive experiments have proven conclusively the correctness of both of these presumptions.

Full discussion of the symptoms and of related conditions in man and other animals will be reserved until the experimental results have been presented. It is sufficient to say here that the defective condition is always clearly marked and easily recognizable, and that in no case have there been doubtful intermediates. Furthermore, such efforts as have been made as yet to rear the defective offspring have been uniformly unsuccessful; these individuals always die within a short time, usually within two weeks of birth.

Origin of Palsied Stock

Later in 1915 palsied offspring were produced by other parents and studies of the pedigrees have shown that such individuals have appeared in three distinct lines

which are unrelated so far as the pedigrees show back to our original stock. This stock came from two sources, a few animals received from Professor Castle, of Harvard University, and somewhat less than a dozen young animals supplied us by our veterinary department, but obtained from a dealer. This stock had multiplied to about forty individuals at the time records were begun on it. The pedigrees show that in all probability there was only one individual, a male, in the Castle stock which might have brought in the palsy character, and since Professor Castle informs us that he has never noticed it in his animals, this individual may with considerable certainty be ruled out as the source of the defect in our experiments. The young animals received from the dealer were all of about the same age and were white spotted, very similar in appearance, which suggests that they may have been related. We are accordingly led to conclude that the character was introduced with this stock and that in all probability it may have traced back to one, or at least only a few, heterozygous animals, and that, furthermore, if there were more than one they were probably related.

INHERITANCE OF THE PALSY CHARACTER

The factor for normality appears to be completely dominant and we have found it impossible to distinguish animals carrying the defective trait from those which do not on the basis of observable behavior or any other characters. The only method of separating the two classes is therefore by breeding tests. Owing to the fact that the affected (recessive) individuals always die, it has been necessary to conduct the experimental tests by the roundabout method of always mating animals to be tested to others known to be heterozygous. If the individual being tested was a homozygous normal no defective offspring would be produced by such a mating, whereas if it was heterozygous they should appear in the usual ratio for Mendelian recessives. We have therefore conducted extensive experiments to determine, (1) the ratio of palsied

offspring when two heterozygotes are mated, (2) the proportion of homozygous to heterozygous individuals among the normal offspring of such matings, and (3) the ratio of homozygous to heterozygous offspring when homozygote was mated to a heterozygote.

Since for practical reasons the number of offspring which can be produced from any particular pair of parents is limited, it became necessary to set a definite arbitrary number which should be taken as the minimum to indicate a fair probability that the animal being tested was homozygous for normality if no recessive young were born. Five was chosen as this minimum, but in every instance larger numbers were obtained where possible. All cases in which less than five normal offspring were obtained without the appearance of a recessive are discarded from the calculations. Furthermore, only six of the thirty individuals rated as homozygous normals on the basis of their breeding behavior had so few as five offspring, and in most cases the number was considerably larger, as is shown in Table I.

TABLE I

ANIMALS RATED AS HOMOZYGOUS NORMAL AND THE NUMBER OF EXCLUSIVELY NORMAL OFFSPRING ON WHICH THE RATING WAS BASED

No. of Animals Tested	No. of Normal Offspring Produced by Each	Total Offspring
6[2]	5	30
3[2]	6	18
1[2]	7	7
1	8	8
1	9	9
4	10	40
6	11	66
1	12	12
1	13	13
2	14	28
1	15	15
1	23	23
1	24	24
1	26	26
Total 30	—	319

[2] Eight of these ten animals died before more offspring could be obtained, one was discarded because of being a poor breeder, and one for some unassigned cause.

Further evidence that this test is fairly reliable is furnished by the fact that in matings of heterozygote to heterozygote affected offspring appeared in litters before five normal young had been born in 84 per cent. of the cases, while in 22 of the 32 matings the recessive appeared in the first litter. The complete data are given in Table II.

TABLE II

Number of Matings	Number of Normal Offspring Produced before Litter Containing Recessive
22	0
3	1
2	4
3	5
2	8
32	

For present purposes we have adopted the symbol *N* to represent a factor for normality; the recessive, palsied animal is therefore *nn*.

1. *Ratio of Palsied Offspring when two Heterozygotes are mated.*—As there appears to be no need of presenting the detailed data of individual matings, the combined results of mating heterozygous animals together are given in the left hand side of Table III. Of the total number

TABLE III

MATINGS *Nn* × *Nn*

	Offspring			Tested Normal Offspring	
	N	*nn*	Born Dead	*NN*	*Nn*
Observed	183	63	36	7	15
Expected	184.5	61.5	—	7.3	14.6

of offspring alive when born (that is, when found) 183 were normal and 63 palsied, an almost exact three-to-one ratio. We, therefore, feel safe in our assumption that the palsied condition is based on a single unit factor difference. The question might be raised as to whether the rather large number of offspring "born dead" might not represent a disproportionate number of palsied young. This does not, however, seem probable for a number of

reasons. In the first place, the palsied animals appear as strong and vigorous when born, and in all respects except for the nervous condition as fully developed as the normal young. This is further borne out by the weights, the weight of the palsied young being as great, indeed averaging slightly more at birth than that of the normals. The weights at birth of the living young from $Nn \times Nn$ matings are shown in Table IV, from which it will be seen

TABLE IV

WEIGHTS AT BIRTH OF LIVE OFFSPRING PRODUCED BY MATINGS $Nn \times Nn$

	Number Weighed	Average Weight in Grams	Number Not Weighed	Total Individuals
Normal males	91	88.61	4	95
Normal females	79	88.68	9	88
Normal males and females combined	170	88.65	13	183
Palsied males	32	92.21	0	32
Palsied females	29	87.96	2	31
Palsied males and females combined	61	90.19	2	63

that 170 normal offspring averaged 88.65 grams, whereas 61 palsied young average 90.19 grams. The slightly greater weight of the latter is probably not significant. These facts seem to indicate strongly that the congenital death rate was not differential with respect to palsy.

2. *Proportion of Homozygous to Heterozygous Individuals among the Normal Offspring of $Nn \times Nn$ Matings.*—Further proof that we were dealing with a single factor difference was provided by tests of the normal offspring from matings of heterozygote to heterozygote. These should, of course, consist of two heterozygous individuals to each extracted homozygous dominant, which should breed as free from the defect as any animals from non-palsy stock. As shown in the right-hand half of Table III, 22 of the 183 normal individuals were tested, of which 7 proved to be *NN* and 15 *Nn*, the theoretical expectations being 7.3 and 14.6, respectively.

3. *Ratio of Homozygous to Heterozygous Offspring from Mating $NN \times Nn$.*—One other type of test was

made, namely, of the normal offspring resulting from the mating of homozygous to heterozygous individuals. The expectation in this case is equality of the classes, and the

TABLE V

MATINGS $NN \times Nn$

	Offspring			Tested Offspring	
	N	*nn*	Born Dead	*NN*	*Nn*
Observed	319	..	36	14	11
Expected	319	0	..	12.5	12.5

actual numbers found in the 25 tests made were 14 *NN* and 11 *Nn*, the expectation in this case being 12.5 in each class (see Table V).

Additional evidence that the extracted homozygous normals are free from palsy "taint" is furnished by three matings of such animals together, from which 31 living offspring have been obtained, all normal.

The foregoing data would appear to be sufficient in number and in closeness of ratios to demonstrate conclusively that congenital palsy in guinea-pigs is inherited in simple Mendelian fashion and depends on a single unit difference, the normal condition being completely dominant to the heterozygote.

SYMPTOMS

A brief description of the typical symptoms has already been given, but for comparison with the same or similar conditions which may be observed by others, it seems desirable to describe the symptoms of the palsy as it occurs in our stock in somewhat greater detail.[3]

A word ought perhaps to be said at this point about the use of the term congenital palsy. The congenital part is evident enough and needs no explanation further than to point out that we use it in the sense of being present at

[3] We wish to express our appreciation of valuable advice and assistance rendered us by Dr. W. J. Meek in connection with this and the following sections of this paper.

time of birth rather than of being contracted at time of birth, which is the connotation sometimes implied in relation to certain infectious diseases. The word palsy is used in the general sense to indicate the broad similarity of the condition in the guinea-pigs to trembling palsy in man. The term is intended to be a neutral one with no implications as to the ultimate cause of the disturbance. The condition perhaps in some ways more closely resembles tetany as manifested in mammals below man, but this term has been avoided as having possibly too specific an implication.

There is considerable variation in the degree to which different individuals are affected. In most cases the victim when discovered shortly after birth is lying on its side slowly moving the legs, twisting the body and lifting the head as if in a vain endeavor to get on its feet. The movement of the fore part of the body, head and forelegs is much more pronounced than that of the hind quarters and hind legs. Some individuals if placed gently on their feet are able to stand, though usually in a strained tense attitude. The difference between this and the normal position may be observed in Fig. 1, ♀ 1089.1 being a palsied individual, while the others are its normal brother and sisters. The photograph is taken from directly above. The affected individual has the feet somewhat spread and the body slightly contorted, while the others are in natural easy attitudes.

If left quietly to itself after being placed on its feet the animal usually stands unsteadily for a few moments and then when it starts to walk falls on its side, with characteristic movements of the legs to be described presently. Some animals are so little affected at birth that they are able with effort to gain their feet themselves, and to walk about in a clumsy, jerky, paralytic fashion. They experience the most difficulty in the control of the hind legs, which appear to be in a hypertonic state and are commonly moved more in a hopping fashion than in steps. A rough classification of 51 palsied animals soon after birth gives the following: 14 unable to rise and unable to stand

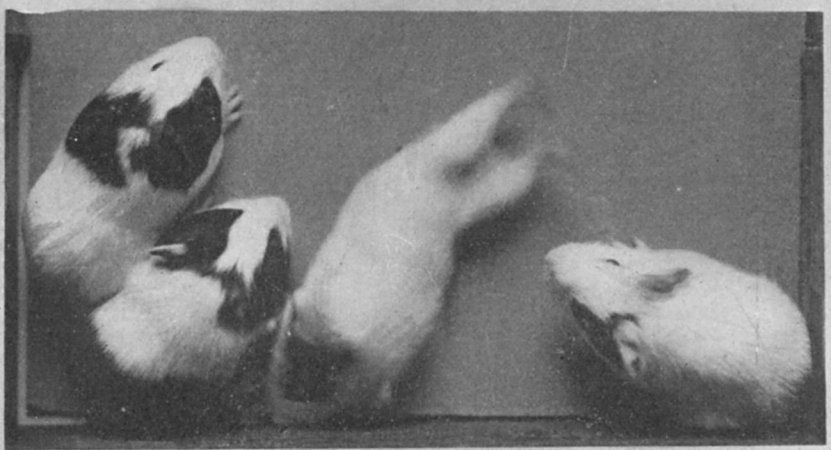
when placed on their feet; 18 able to stand but unable to walk; 5 able to walk when placed on their feet but unable to arise unaided; and 14 able to get up and to walk. It should be recalled that in all cases the symptoms grow progressively worse, leading to the most severe conditions, and to death in a week or two at most.

Breathing appears to be normal, as is also control of the muscles of the jaws and throat, for the less affected animals sometimes eat solid food, and those that are able to walk may suckle the mothers. Such individuals increase in weight for a time as rapidly as normal young, but with the progress of the disease they become unable to obtain nourishment, and consequently decline. We are unable to state at present whether death is attributable finally to starvation, or whether it is a direct sequel of the disease.

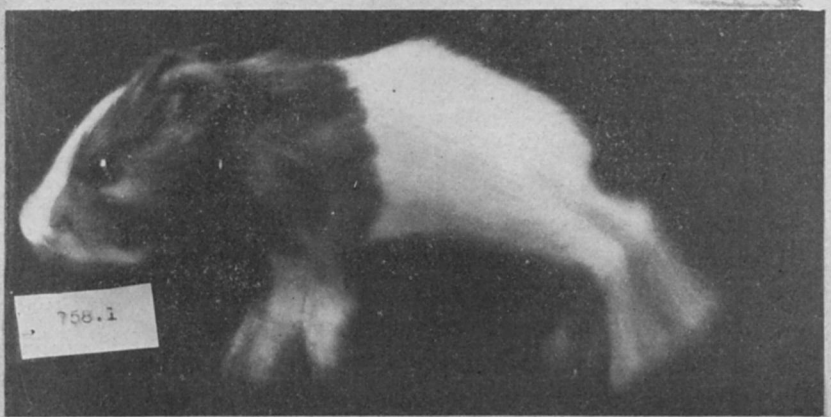
The most striking phenomenon in connection with the disease is the reaction to stimuli, particularly to auditory stimuli. This may be best observed in animals that can stand when placed on their feet but are able to walk only with great difficulty, if at all. If such an animal is placed on its feet and a sharp sound is then made, such as clapping the hands, snapping the fingers, or squeaking with the lips, the reaction is definite and immediate—the subject jumps upward and forward, due to a sudden stiffening, particularly of the hind legs, then falls on its side, the whole body shaking to some extent, but the legs exhibiting strong clonic spasms. To the same stimulus normal individuals give merely a slight start, and then sit unconcernedly as before. This result is clearly shown in Fig. 2, which depicts the same litter as Fig. 1, but following a stimulus which has thrown the affected individual into a spasm as described. Fig. 3 is a short time-exposure of an animal in a spasm lying on its side. The photograph shows clearly the movement of the feet.

Visual stimuli have relatively little effect in producing the above-mentioned reaction. Even if the hand is brought rapidly down to near the animal's eyes it seldom responds. The same is true for mechanical stimuli, the reaction occurring only if the stimulation is severe. Af-

1 ♂1089.3 NN ♀1089.4 Nn ♀1089.1 nn ♀1089.2 Nn



2 1089.3 1089.4 1089.1 1089.2



3 758.1

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fected animals which are fairly able to walk may not fall over even as a result of an auditory stimulus. They give a jump, much more pronounced than the start of normal individuals, but manage to stay on their feet. Furthermore, even the more affected ones become less sensitive to repeated stimulation, and may after several reactions fail to respond sufficiently to make them lose their balance.

In the more severe stages the reaction appears to simulate intentional tremor, in that it follows attempts at voluntary movements of the hind legs. In less severe cases the animal can use the legs if free from other nervous excitation. It would appear therefore that the condition is induced by sudden nervous excitement, the degree of the stimulus necessary to cause complete lack of muscular control depending on the stage of progress of the affection.

The severe spasms commonly last but a few moments. If a guinea-pig stiffened out in one of the spasms is taken in the hand it can soon be felt to relax, following which it either lies quiet or makes slow movements of the head and to some extent of the legs as previously described.

ETIOLOGY

A number of possibilities suggest themselves as causes of the disease described in this paper, and these will be discussed in order.

1. As mentioned in the following section, digestive disturbances may cause in sheep a condition very similar in many of its symptoms to the spasm of our guinea-pigs. Is it not possible that these were originally induced by some similar cause? It is true that at times, especially in the early part of the work, we have had some trouble from improper feeding, notably when we attempted to substitute sugar beets for carrots and cabbage. While, however, inadequate diet may cause scurvy and other effects, we have no reason to believe that it ever produces a condition which could be mistaken for the congenital palsy. Furthermore, palsy never occurs in the descend-

ants of two homozygous normal individuals, even though their feeding and care is in all respects similar to that of the others. In other words, the disease has behaved strictly in accord with the known principles of heredity since it has been under observation, and we have every reason to believe that it has not appeared spontaneously during that time. This would mean then that if the disease was due to nutritive conditions, it must have had its inception in the stock before we received it, or within a very short time thereafter at latest.

The evidence that heritable defects of this sort may be induced by external conditions is very meager at best, Stockard has produced somewhat similar nervous defects in guinea-pigs by the administration of alcohol, but while he claims that these are heritable, he has not, so far as we are aware, shown that any of them are inherited in strict Mendelian fashion as is the defect with which we are concerned. We are therefore led to believe that this character in our stock has not been induced by nutritional or other environmental causes, but that it is due to a factor mutation similar to those which have been studied so thoroughly in domesticated and experimental animals and plants in recent years, and for which there is at present no assignable cause.

2. It might perhaps be assumed that the palsied individuals are due to unfavorable uterine conditions and consequent abnormal fœtal development. The occurrence of "runts" in swine and in other animals which produce large litters show that the uterine conditions are not the same for all the individuals in a litter. Some doubtless have a poorer maternal blood supply than others, or they may be crowded, or twisted into a position unfavorable for growth. That these are not factors in the present case seems demonstrated, however, by the fact that the palsied animals are on the average fully as large and well developed at birth as their litter mates (see Table IV).

3. The necessity of inbreeding the original stock in order that the recessive palsy condition should appear is apparent; but it might be maintained that this inbreeding

in itself was perhaps the cause of the disease. All modern studies on inbreeding, however, seem to strengthen the conclusion that while inbreeding may, by the "concentration" or production of unfavorable character combinations, and particularly by the loss of important physiological factors which are necessary to the well being of the individual, result in lowered vitality and in the appearance of various defects, it is nevertheless a means rather than a cause of bringing these into expression.

Further evidence that the palsy was not produced by the inbreeding as such is furnished by the fact that the lines in which it appeared were no more inbred than many other lines that have been carried on in the laboratory in connection with other problems, but in which no tendency to such a defect has manifested itself. Our whole stock, in fact, of some 2,200 litters and over 5,000 offspring has all descended from not more than 50 original animals, and as has already been stated, there is reason to believe that some of these were related. In order to show the intensity of the inbreeding in some cases, it may be mentioned that in one experiment a male was bred back to his daughters for four successive generations, and with no apparent ill effects. Inbreeding as a predisposing cause may therefore be ruled out.

4. The spasms which form the characteristic reaction of the palsied animals are clearly due to lack of nervous control, especially when voluntary movements of the legs are attempted, and under excitement. It may therefore be that there is some heritable defect of the central nervous system. Examinations which have been made for us by Dr. C. H. Bunting have, however, shown no lesions of the nervous system to which these effects could be attributed.

5. Disturbances of some of the glands which supply internal secretions are known to produce nervous irritability and conditions of spasm and tetany. Particularly is this true of the parathyroid, and some of the symptoms accompanying disturbances of this gland resemble to a certain extent, at least superficially, the con-

ditions in the guinea-pigs. Dr. Bunting is making a study of this phase of the question, and reports that "thus far the only anatomical difference between affected and normal animals of the same litter, that has been noted, has been a definite hypoplasia of the parathyroid tissue in the abnormal animals." He will, however, report more fully later.

For the present, therefore, we must be content with the statement that the congenital palsy is due to a factor mutation, the cause of which is unknown; nor do we understand what its action is on the animal organism to produce the nervous symptoms described.

Discussion

A number of nervous defects are known in man and the lower animals which have certain points of resemblance to congenital palsy as it occurs in our guinea-pigs, but we have been unable to find any condition which agrees closely enough in details so that the two could be considered identical. A list of some of these follows, with brief mention of resemblances and points of difference.

Pigeon.—Tumbling in pigeons appears to be due to lack of nervous control of the muscles and associated to some extent with certain voluntary efforts. This is especially noticeable in Parlor Tumblers, which turn back somersaults when they attempt to fly. The condition is greatly exaggerated by excitement. Further similarities are that the tendency to tumble increases with age, to a certain point at least, and that it behaves in a general way as a recessive to normal flight, though the crossbreds are usually intermediate and there appears to be no sharp segregation in F_2. Tumbling, unlike congenital palsy, does not seem to affect the legs particularly, and does not interfere with normal life processes sufficiently to be lethal if the birds are given adequate protection and care.

The condition described by Riddle (1918) as *ataxia* in pigeons would appear to correspond very closely in symptoms to the more pronounced cases in Parlor Tumblers.

There would appear to be also some resemblance to the tumbling and shaking of the Fantail (French *Trembleur*). Riddle states that the "character is, with some irregularities, a Mendelian recessive." His inference that it may have been produced by "reproductive overwork" seems inconclusive.

In connection with experiments on the homing ability of pigeons Hurst (1913) speaks of obtaining "*feeble-minded*" birds, as follows:

> Results show that incompetent or feeble-minded pigeons may be bred from competent or intelligent parents, and it is interesting to find that feeble-mindedness behaves as a recessive character in birds as well as in man.
>
> Fortunately, or unfortunately, it is much more difficult to get offspring from the feeble-minded in Pigeons than in Man.

Mouse and Rat.—The well-known "waltzing" of the waltzing mouse is probably of the nature of a nervous disorder, either directly or indirectly. It is a simple Mendelian recessive.

Bonhote (1912) at a meeting of the Zoological Society of London "exhibited living specimens of rats (*Mus rattus*) which he had bred in the course of his experiments, and which showed the 'waltzing' character well known in a variety of the domestic mouse, but which had not hitherto been recorded in rats."

Rabbit.—We have in our possession a rabbit which is now several years old, and which has since it was young exhibited characteristic circus movements, or "waltzing," very similar to the activities of the waltzing mouse. This character appeared sporadically and we have been unable to find that it is heritable, even though we have repeatedly bred this male's daughters to their own brothers and back to him. He appears normal in other respects except that one eye seems somewhat distorted, which may have something to do with his behavior. This case differs from the waltzing mouse in that it is probably not heritable, and certainly is not a simple Mendelian recessive.

Guinea-Pig.—Some of the various defects in guinea-

pigs described by Stockard and ascribed to the inherited effects of alcohol treatment of the original parents, have symptoms somewhat resembling those of congenital palsy. His descriptions of the symptoms and behavior of his animals are, unfortunately, inadequate for detailed comparison of our cases with his. One point seems certain, however, namely, that while the symptoms exhibited by our animals are relatively constant, he has obtained in his affected lines a great variety of nervous defects and anatomical abnormalities, all of which he attributes to degeneration caused by the alcohol. To mention those relating to nervous disorders, he speaks of the defective animals as being "very shy and excitable" (1912, p. 22), and says further: "it is a point of some interest that all of the young animals that died showed various nervous disturbances, having epileptic-like seizures, and in every case died in a state of convulsion." Again (1913, p. 663) he speaks of an animal which died when one day old, "having been in a constant tremor since its birth; another lived for nine days *but whenever it attempted to walk it was seized with spasmodic contractions;* the third specimen exhibited the same nervous manifestation and was completely eyeless." In a later paper (1916, p. 15) he says that *paralysis agitans* is very common among the F_1, F_2, and F_3 animals, apparently applying this term to some of the symptoms mentioned in earlier papers, and adds that "paralyzed limbs are often observed, the animals being unable to stand or walk."

While some of the above symptoms approximate those of congenital palsy, they seem to partake for the most part either of a general nervous irritability or else of a definite paralysis. Furthermore, while Stockard bases his conclusion that the general defect that produces these various conditions is hereditary on the fact that they continue to appear in his treated lines, but not in the parallel control lines, he has not so far as we are aware, found any tendency for the condition to be inherited in any definite manner or proportions conformable with Mendelian rules.

It is not clear, however, that he has made any systematic matings in an endeavor to ascertain this point.

While we do not mean to imply that in Stockard's experiments the initiation of the various defects and abnormalities he describes may not have been due to the alcohol treatment, it is nevertheless of interest to note that these same defects and abnormalities appear from time to time in our normal stock. We can, in fact, match his conditions—almost case for case for all that he has described—with offspring of our stock that has had the best care we could give it. That our stock is as a whole in no way degenerate is indicated by its prolificacy (average size of 863 litters = 2.71), its low mortality rate, and the fact that our animals are if anything above the general run of guinea-pig stock, as attested by reports from the various hygienic and other laboratories to which our surplus has gone. The point of special interest is that these various abnormalities are entirely independent of the congenital palsy, for they appear no more frequently in the "palsy" stock than elsewhere.

Goat.—Hooper (1916) has described a case in goats which has some strong points of resemblance to the behavior in the guinea-pigs, although in the former the conditions are not so severe as to cause the death of the animals. He says:

> There is a peculiar breed of goats raised in central and eastern Tennessee. When suddenly frightened the hind legs become stiff and the animal jumps along until it recovers and trots off normally or if greatly frightened the front legs become stiff also and the goat falls to the ground in a rigid condition. They have received the name of "stiff-legged" or "sensitive" goats.

Experiments were to be begun on the inheritance of the character, but results have not to our knowledge been reported.

Sheep.—A condition in sheep with symptoms somewhat resembling those in "palsied" guinea-pigs and even more the goats just mentioned is described by Jones and Arnold (1917). Affected animals are able to walk, but

when excited they run in a stumbling fashion and finally the legs stiffen out and the animal falls on its side. This affection is, however, not heritable, but has been demonstrated by these investigators to be due to nutritional disturbance, caused by a diet consisting too largely of pampas grass.

When there is a liberal amount of grass the actual number of cases is small. After a long continued drought when the fine grass supply is short, the number of sick animals is large. The mortality varies considerably, young sheep seeming to suffer most.

Man.—Among the numerous confusing and complex nervous disorders in man there are several with certain similarities to congenital palsy of the guinea-pigs. We have not attempted an exhaustive survey of this field, but list a few of them with remarks on resemblances or dissimilarities. In some cases it is difficult to tell whether the descriptions refer to the same or different affections, the synonymy not being clear. The comparison with congenital palsy is also often uncertain owing to the indefiniteness of the descriptions of symptoms. No attempt at completeness has been made in the matter of references, citations being added merely for giving authority for the statements made.

Feeble-mindedness (Davenport, 1911), *epilepsy* (Davenport, 1911; Davenport and Weeks, 1911; Weeks, 1915) and some forms of *insanity* (Davenport, 1911) resemble congenital palsy in being definitely recessive in inheritance, but show no close similarities in other symptoms.

SIMILARITIES	DIFFERENCES
Paralysis agitans (Parkinson's disease). (Curschmann, 1915.)	
Tremor of muscles.	Appears late in life.
Progresses in severity with course of disease.	Constant trembling.
	More often in male sex.
Habitual tremor. (Curschmann, 1915; Dana, 1887.)	
Occurs early in life.	Not congenital.
Subsides when patient is at rest.	Affects mostly hands and head.
Increased by voluntary movements and excitement.	Shallow oscillations.
Tendency to be hereditary? (Occurs mostly in neuropathically inclined individuals.)	May disappear.

Familial tremor. (Curschmann, 1915.)

Hereditary.	Not congenital.
Usually appears in youth.	Sometimes improvement.
Diminishes at rest.	
Affects mostly arms and legs.	
Progressive in its course.	
Treatment powerless.	

Tetany. (Curschmann, 1915.)

"Intentional" in some cases.	Tonic spasms.
Easily induced by stimuli.	Hands and arms mostly.
Legs often attacked.	Spasm duration long.
Idiopathic tetany incurable.	Infection indicated.

Progressive lenticular degeneration. (Wilson, 1912; Spiller,[4] 1916.)

Bilateral.	Not congenital.
Affects both extremities.	Accompanied by cirrhosis of liver?
Increase with volitional movement.	Tonic spasticity of face and limbs.
Reflexes preserved.	
Always fatal.	
Familial.	

Aplasia axialis extra-corticalis congenita. (Merzbacher, 1908; Batten and Wilkinson, 1914.)

Congenital or in first three months.	Affects chiefly males.
Hereditary.	Slowly if at all progressive.
	Symptoms constant.
	Not so fatal.

Paramyotonia congenita. (Eulenberg, 1886.)

Congenital.	Tonic spasms.
Hereditary.	Not always bilateral.
	Last for hours.
	Apparently dominant.

It is clear that none of the above-mentioned conditions can be considered as identical with congenital palsy. The most common similarity is that several of them are known to be recessive in inheritance, but they all differ in other symptoms. Congenital palsy differs from any of the other conditions in being definitely congenital and running a brief course terminating in death at an early age.

In conclusion it may be pointed out that while the data may never be sufficiently complete in man, it may be pos-

[4] According to Spiller the conditions attributed to disease of the lenticular nucleus are numerous, including the pseudo-sclerosis of Westphall and Strümpell, Huntington's chorea, Parkinson's disease, and a number of others.

sible in animals where breeding experiments can be conducted, to use the inheritance method for separating nervous diseases in which the symptoms are so similar as to be confusing, or even identical. For example, let us suppose that a recessive neurosis similar to congenital palsy should appear in another line of guinea-pigs. If animals heterozygous for it were mated to heterozygous individuals of our stock and they produced affected offspring in a one-to-three ratio, it would be good evidence that we were dealing with the same heritable trait in both strains. If, however, the disease in the new line was genetically different, a different ratio of offspring would be expected, presumably nine normal to seven neurotic individuals, assuming that there was no linkage of the two genes concerned. It is possible that even in man when the family histories are sufficiently complete the method of genetic analysis may help in the differentiation of neuroses characterized by symptoms which are confusingly similar.

Summary

1. A definite neurosis appeared in our guinea-pig stock in 1914, characterized by clonic spasms, particularly of the legs. When in a spasm the animals lie on their sides in a helpless condition. This state is induced by various stimuli, but especially by those of a sharp auditory nature, and also by attempted volitional movements of the legs.

2. The affected animals are fully up to average weight when born, and appear to be normal in all other respects. While different individuals vary with respect to the intensity of the symptoms at birth, they are always easily distinguished from normal young, and in all cases the disease runs a short progressive course, terminating in death within about two weeks at most.

3. This defect, which we have called congenital palsy, is definitely heritable. It is a simple Mendelian recessive, and normal and affected offspring are produced by two

heterozygous parents in the ratio of three normal to one affected.

4. It has been shown that heterozygous animals mated to normals produce offspring of the same classes as themselves in equal numbers. Furthermore, it has been proven that homozygous dominants can be extracted from heterozygous parents and that they show no more tendency to transmit the disease than individuals of normal unrelated stock.

5. Heterozygous animals are entirely normal in their reaction and can be told from the homozygous only by breeding tests.

6. A survey of the literature relating to nervous defects in man and other animals does not reveal any condition corresponding exactly to congenital palsy. Some of the conditions in pigeons, rodents and in man are similar in that they are recessive in inheritance.

REFERENCES

Batten, F. E., and D. Wilkinson.
1914. Unusual Type of Hereditary Disease of the Nervous System (Pelizaeus-Merzbacher), Aplasia, Axialis Extra-corticalis Congenita. *Brain*, Vol. 36, pp. 341–351.

Bonhote, J. L.
1912. [On Waltzing Rats.] *Proc. Zool. Soc. Lond.*, March, 1912, pp. 6, 7.

Curschmann, H. (Editor.)
1915. Text-book on Nervous Diseases. English edition edited by Charles W. Burr. Philadelphia, 2 vols., xx + 1132 pp.

Dana, C. L.
1887. Hereditary Tremor, a Hitherto Undescribed Form of Motor Neurosis. *Amer. Jour. Med. Sci.*, Vol. 44, p. 386.

Davenport, C. B.
1911. Heredity in Relation to Eugenics. New York, Henry Holt and Company. Pp. xi + 298.

Davenport, C. B., and D. F. Weeks.
1911. A First Study of Inheritance in Epilepsy. *Jour. Nerv. and Mental Dis.*, Vol., 38, No. 11, pp. 641–670. (Bull. No. 4, Eugenics Record Office, pp. 1–30.)

Eulenberg, A.
1886. Über eine familiäre durch 6 Generationen verfolgbare Form kongenitaler Paramyotomie. *Neurol. Zentralbl.*, p. 265.

Hooper, J. J.
1916. A Peculiar Breed of Goats. *Science*, N. S., Vol. 43, No. 1112, p. 571.

Hurst, C. C.
1913. British Association for the Advancement of Science. Birmingham Meeting. 1913. Visit of Sections D, K, and M, to the Burbage Experiment Station of Applied Genetics, on Tuesday, September 16. Notes on the experiments by the Director. 8 pp.

Jones, F. S., and J. F. Arnold.
1917. Staggers in Sheep in Patagonia. *Jour. Exper. Med.*, Vol. 26, pp. 805–823, 4 pls.

Merzbacher, L.
1908. Weitere Mitteilungen über eine hereditär-familiäre Erkrankung des Zentralnervensystems. *Med. Klinik.*, Bd. 4, pp. 1952–1955.

Spiller, W. G.
1916. The Family Form of Pseudo-sclerosis and other Conditions Attributed to the Lenticular Nucleus. *Jour. Nerv. and Mental Dis., Vol.* 43, pp. 23–26.

Stockard, C. R.
1912. An Experimental Study of Racial Degeneration in Mammals Treated with Alcohol. *Arch. Internal Med.*, Vol. 10, pp. 369–398 (separate, pp. 1–30).
1913. The Effect on the Offspring of Intoxicating the Male Parent and the Transmission of the Defects to Subsequent Generations. AMER. NAT., Vol. 47, pp. 641–682.
1916. The Hereditary Transmission of Degeneracy and Deformities by the Descendants of Alcoholized Mammals. *Interstate Med. Jour.*, Vol. 23, No. 6, pp. (of separate) 1–19.

Riddle, Oscar.
1918. A Case of Hereditary Ataxia (?) in Pigeons. *Proc. Soc. Exper. Biol. and Med.*, Vol. 15, pp. 56–58.

Weeks, D. F.
1915. Epilepsy with Special Reference to Heredity. *Jour. Med. Soc. New Jersey*, pp. (of separate) 1–8.

Wilson, S. A. K.
1912. Progressive Lenticular Degeneration, a Familial Nervous Disease Associated with Cirrhosis of the Liver. *Brain*, Vol. 34, pp. 295–509.